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L9: Entry 1 of 1 File: USPT Jan 23, 1990

DOCUMENT-IDENTIFIER: US 4895796 A
TITLE: Identification of NK cells and cytotoxic T lymphocytes

YEAR ISSUED (1):
1990

Brief Summary Text (7):
Whereas T cells can be readily identified by their reactivity with anti-CD3 antibodies, there has been no simple and sensitive method for the identification or enumeration of NK cells using a single labeling reagent. It is well known that most NK cells express the CD16 antigen. CD16 is a 50-70 kD glycoprotein that is associated with a receptor for IgG. Numerous antibodies have been produced against CD16, including anti-Leu-11a, VEP13, B73.1, L23 and others (Lanier et al., J. Immunol. (1983) 131:1789; Perussia et al., J. Immunol. (1983) 130:2133; Perussia et al., J. Immunol. (1983) 130:2142; Rumpold et al., J. Immunol. (1982) 129:1458; Lanier et al., J. Immunol. (1986) 136:4480). However, it has been demonstrated that CD16 cannot be detected on all NK cells, particularly NK cells that have been activated in culture. Moreover, in certain circumstances CD16 can also be expressed on T lymphocytes (Lanier et al., J. Exp. Med. (1985) 162:2089). Most NK cells express another glycoprotein on the plasma membrane that is identified by the anti-Leu-19 monoclonal antibody, an antibody commercially available from the Becton Dickinson Monoclonal Center, Inc. Anti-Leu-19 recognizes a glycoprotein of about 160 kD (GP160) that is also recognized by the NKH-1 monoclonal antibody (Lanier et al., J. Immunol. (1986) 136:4480). However, neither anti-Leu-19 nor NKH-1 react exclusively with NK cells but can also react with other non-lymphocyte cell types (Lanier et al., J. Immunol. (1987) 138:2019). Anti-Leu-19 also reacts with a unique minor subset of T lymphocytes, at least some of which kill without MHC restriction (Lanier et al., J. Immunol. (1986) 136:4480). Finally, the amount of the antigen recognized by anti-Leu-19 on the plasma membrane of NK cells is often low, making it difficult to precisely identify and enumerate the number of NK cells in a mixed cell population, such as blood or other tissues.

Drawing Description Text (3):
The FIGURE is a graph showing the fluorescence of cells labeled with FITC-anti-Leu-4 (CD3) versus fluorescence of cells labeled with PE-anti-Leu-19 (GP160) plus PE-anti-Leu-11c (CD16).

Drawing Description Text (6):
Cell surface antigens on lymphocytes and NK cells have been identified using several systems of nomenclature. For example, the antigen identified as Leu-4 in this specification is also known as the CD3 antigen using the CD nomenclature for differentiation antigens. Similarly, the Leu-11 antigen is known as CD16. The relationship of the antigen recognized by anti-Leu-19 to the CD cluster antigens has not been established, but the Leu-19 antigen appears to be the same as the antigen identified by the NKH-1 antibody. For the purposes of this application, this third antigenic material is referred to as GP160. The CD and GP160 designations refer to the entire antigen and are more general than the Leu designations, which are derived from a series of monoclonal antibodies that recognize specific determinants on the antigens. In some instances in this discussion of the invention, reference is made to the Leu designations while in other instances the more general CD and GP160 designations are used. While in some instances it will be clear from the context that either the general or the specific case is intended, in many cases the two terms are used interchangeably.

Drawing Description Text (7):

The Leu system of nomenclature arose from the use of monoclonal antibodies that reacted specifically with individual antigens present on the surface of cells. Anti-Leu-4 reacts with CD3, a complex of at least three proteins of 20-30 kD (Kan et al., J. Immunol. (1983) 131:536; Borst et al., J. Immunol. (1982) 128:1560). Anti-Leu-11 specifically reacts with the CD16 antigen. CD16 is a 50,000-70,000 Dalton protein that is associated with the Fc receptor for IgG present on NK cells and neutrophils. For a detailed discussion of the antigen and its reactivity, see, for example, Lanier et al., J. Immunol. (1983) 131:1789; Perussia et al., J. Immunol. (1983) 130:2133; Perussia et al., J. Immunol. (1983) 130:2142; Rumpold et al., J. Immunol. (1982) 129:1458; and Perussia et al., J. Immunol. (1984) 133:180. GP160, the antigen recognized by anti-Leu-19, is a glycoprotein with a molecular weight of about 160,000 Daltons and an unknown function. For a detailed description of its properties and reactivity, see, for example, Lanier et al., J. Immunol. (1986) 136:4480; Griffin et al., J. Immunol. (1983) 130:2947 and Hercend, J. Clin. Invest. (1985) 75:932. GP160 has not yet been given a CD name by the Leukocyte Differentiation Antigen Workshop Committee of the World Health Organization. Note that in prior reports the molecular weight was overestimated; more recent studies indicate that the relative mobility is approximately 160,000 kD.

Drawing Description Text (8):
Monoclonal antibodies useful in the practice of the present invention can be prepared by standard techniques as descried below. Anti-Leu-11 can be produced by immunizing mice with human peripheral blood, low-buoyant-density lymphocytes or granulocytes and fusing the immune splenocytes with a myeloma cell line. The antigenic specificity for Leu-11 in the resulting hybridomas can be determined by competitive binding studies and immunoprecipitation of the CD16 antigen. Anti-Leu-19 can be prepared in a similar manner by immunizing mice with the KG1a cell line (Koeffler et al., Blood (1980) 61:1222), fusing the immune splenocytes with a myeloma cell line, and selecting cells that produce an antibody reactive with the NKH-1 antigen. Anti-Leu-4 can be produced by immunizing mice with human thymocytes or peripheral T lymphocytes, fusing the immune splenocytes with myeloma cell line, and selecting cells that produce an antibody reactive with CD3. Antigenic specificity can be determined by competitive binding studies and immunoprecipitation of CD3 antigen (Beverly and Callard, Eur. J. Immunol. (1981) 11:329; Kung et al., Science (1979) 206:347).

Drawing Description Text (13):
It is particularly preferred to use two different fluorescent labels as the first and second label used in the method of the invention. Use of different fluorescent labels allows easy detection and cell sorting by flow cytometry using automated equipment. A preferred pair of fluorescent labels is fluorescein (conjugated from the isothiocyanate, FITC) and phycoerythrin (conjugated to the antibody with SPDP, which is N-succinimidyl-3-(2-pyridyldithio)propionate). Other suitable cross-linkers and coupling techniques for attaching fluorophores to antibodies can be used. Either fluorescein or phycoerythrin can be used as the first detectable label with the other being used as the second detectable label as long as one label is used with anti-Leu-4 and the other label used for both anti-Leu-11 and anti-Leu-19.

Drawing Description Text (15):
T lymphocytes and NK cells are distinguished by their ability to bind with the two reagents. All cells which react with anti-Leu-4 are identified as T lymphocytes whether or not they also react with anti-Leu-11 and/or anti-Leu-19. Those cells which react with both anti-Leu-4 (Reagent 1) and anti-Leu-19 or anti-Leu-11 (Reagent 2) form a subset of T lymphocytes, some of which mediate non-MHC restricted cytotoxic function. Lymphoid cells which react with Reagent 2 (anti-Leu-11 and/or anti-Leu-19) but not with Reagent 1 (anti-Leu-4) are identified as NK cells.

Detailed Description Text (5):
Anti-Leu-19, an IgG1, .kappa. MAb, was produced by the My31 hybridoma cell line. My31 was derived by immunizing (C57BL/6 x BALB/c) F.sub.1 mice with the KG1a cell line (described in Koeffler et al., Blood (1980) 61:1222), fusing the immune splenocytes with the SP2/0 myeloma cell line, and selecting for antigenic specificity using the indicated antigen.

Detailed Description Text (18):
1. Use of a single PE anti-Leu-19 (GP160) reagent overestimates the proportion of NK cells, since some T cells can express Leu-19. By combining PE anti-Leu-19 with FITC anti-Leu-4 (CD3), it is possible to identify the unique T cells expressing both CD3 and Leu-19, and to more precisely enumerate the NK cells that stain with PE anti-Leu-19 but not FITC anti-CD3.

Detailed Description Text (20):
3. Use of a single PE anti-CD16 (Leu-11) reagent can also underestimate the proportion of NK cells in a population. A population of NK cells in normal blood, as well as some activated NK cells, do not express CD16. However, these CD16 negative NK cells have been shown to express Leu-19. Therefore, by mixing PE conjugated anti-Leu-11 and PE anti-Leu-19 and using this mixed PE conjugated antibody combination in conjunction with the FITC anti-CD3, it is possible to identify substantially all NK cells, including both CD16-,Leu-19+and CD16+,Leu-19+NK cells. Using this novel combination of reagents, it is possible to simultaneously identify and enumerate total T cells (CD3+cells), unique T cells expressing either CD16 and/or Leu-19, and total NK cells (CD3-, Leu-19+and/or CD16+cells).

Detailed Description Text (22):
An illustration of peripheral blood mononuclear cells stained with a first reagent of the invention (FITC conjugated anti-Leu-4 (CD16)) and a second reagent of the invention (consisting of a mixture of PE conjugated anti-Leu-11 (CD16) and PE conjugated anti-Leu-19) is presented in the FIGURE. Samples were analyzed by flow cytometry, and correlated fluorescence of the lymphocyte fraction of mononuclear cells is shown as a contour plot. The display is divided into quadrants. Unstained cells (non-T, non-NK cells) are present in the lower left quadrant, NK cells are present in the upper left quadrant (stained with PE anti-Leu-11 and/or Leu-19, but not FITC anti-Leu4), T cells are present in the lower right quadrant (stained with FITC anti-Leu-4, but not PE anti-Leu-11 or Leu-19), and the unique Leu-11 and/or Leu-19 positive T cells are present in the upper right quadrant (stained with both FITC and PE dyes).

CLAIMS:

4. The method of claim 1, wherein anti-CD16 and anti-GP160 are anti-Leu-11 and anti-Leu-19 monoclonal antibodies, respectively.

16. The reagent mixture of claim 11, wherein said anti-GP160 is monoclonal anti-Leu-19.

STIC-ILL

From: Canella, Karen
Sent: Tuesday, March 04, 2003 5:02 PM
To: STIC-ILL
Subject: ill order 10/021,741

Art Unit 1642 Location 8E12(mail)

Telephone Number 308-8362

Application Number 10/021,741

1. Immunology, 2000 May, 100(1):77-83

2. Immunological Reviews, 2001 Jun, Vol. 181, pp. 234-249

3. Journal of Immunology, 1993 Jul 1, 151(1):60-70

4. Natural Immunity, 1998 Feb, Vol. 16, No. 2-3, page 75

5. Tissue Antigens, 1999 Jul, 54(1):27-34

6. European Journal of Immunology:
   2000 Mar, 30(3):787-793
   2000 Dec, 30(12):3718-3722

7. BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:448599 BIOSIS
DOCUMENT NUMBER: BR41:86334
TITLE: 2B4 ANTIGEN IS INVOLVED IN THE NON-MHC-RESTRICTED CYTOTOXICITY MEDIATED BY NK AND T CELLS.
AUTHOR(S): GARNI-WAGNER B A; PUROHIT A; BENNETT M; KUMAR V
CORPORATE SOURCE: UNIV. TEX. SOUTHWESTERN MED. CENT., DALLAS, TEX., USA.
SOURCE: SEVENTH INTERNATIONAL WORKSHOP ON NATURAL KILLER CELLS, STOCKHOLM (LIDINGO), SWEDEN, JUNE 4-7, 1991: NAT IMMUN CELL GROWTH REGUL, (1991) 10 (3), 173.
CODEN: NICRDR. ISSN: 0254-7600.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

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   FILE SEGMENT: BR; OLD
   LANGUAGE: English

QR180, T55
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   CODEN: NICRDR. ISSN: 0254-7600.
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STIC-ILL

QR185.2.N37

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   CODEN: NICRDR. ISSN: 0254-7600.
   DOCUMENT TYPE: Conference
   FILE SEGMENT: BR; OLD
   LANGUAGE: English

QR180.I5
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   CODEN: NICRDR. ISSN: 0254-7600.
   DOCUMENT TYPE: Conference
   FILE SEGMENT: BR; OLD
   LANGUAGE: English

L5 ANSWER 5 OF 7 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000270067 MEDLINE
DOCUMENT NUMBER: 20270067 PubMed ID: 10809962
TITLE: Expression and functional activity of the very late activation antigen-4 molecule on human **natural killer** cells in different states of activation.
AUTHOR: Macias C; Ballester J M; Hernandez P
CORPORATE SOURCE: Immunology Department, Institute of Hematology and Immunology, Habana, Cuba.
SOURCE: IMMUNOLOGY, **(2000 May)** 100 (1) 77-83.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000531

AB In the present study we describe the expression and functional activity of the alpha4beta1 heterodimer molecule on human **natural killer** (**NK**) cells. Flow cytometric analyses showed that fresh and activated **NK** cells expressed high levels of very late activation antigen-4 (VLA-4) molecules. These cells bound to fibronectin (FN) and to its 38 000-MW proteolytic fragment through the VLA-4 integrin that was blocked with HP2/1 anti-alpha4 monoclonal antibodies (mAbs) and with the FN peptide fragment **CS1**. No inhibitory effects were observed in the presence of anti-alpha5 mAb, FN peptide fragment CS2 or other irrelevant mAb. Fresh **NK** cells were unable to aggregate, despite their expression of VLA-4, and only activated (cultured and lymphocyte-activated killer cells) **NK** cells showed homotypic aggregation with HP1/7 and HP2/4 anti-alpha4 mAb related to cellular activation. These results underline new evidence of how **NK** cells in different states of activation maintain different constitutive levels of alpha4beta1 integrin activity, and highlight the possibility of a different functional regulation by the cells bearing VLA-4, in the expression of these epitopes and their ability to interact with their ligands.

ordered

L5 ANSWER 4 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001468532 MEDLINE
DOCUMENT NUMBER: 21404056 PubMed ID: 11513145
TITLE: 2B4 (CD244) and **CS1**: novel members of the CD2 subset of the immunoglobulin superfamily molecules expressed on **natural killer** cells and other leukocytes.
AUTHOR: Boles K S; Stepp S E; Bennett M; Kumar V; Mathew P A
CORPORATE SOURCE: Department of Molecular Biology and Immunology and Institute for Cancer Research, University of North Texas Health Science Center, Fort Worth 76107-2699, USA.
CONTRACT NUMBER: AI25041 (NIAID)
AI38938 (NIAID)
SOURCE: IMMUNOLOGICAL REVIEWS, **(2001 Jun)** 181 234-49.
Ref: 138
Journal code: 7702118. ISSN: 0105-2896.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20020220
Entered Medline: 20020219

AB 2B4 is a member of the CD2 subset of the immunoglobulin superfamily molecules expressed on **natural killer** (**NK**) cells and other leukocytes. It is the high affinity ligand for CD48. Engagement of 2B4 on **NK**-cell surfaces with specific antibodies or CD48 can trigger cell-mediated cytotoxicity, interferon-gamma secretion, phosphoinositol turnover and **NK**-cell invasiveness. The function of 2B4 in CD8+ T cells and myeloid cells remains unknown. The cytoplasmic domain of 2B4 contains unique tyrosine motifs (TxYxxV/I) that associate with src homology 2 domain-containing protein or signaling lymphocyte activation molecule (SLAM)-associated protein, whose mutation is the underlying genetic defect in the X-linked lymphoproliferative disease (XLPD). Impaired signaling via 2B4 and SLAM is implicated in the immunopathogenesis of XLPD. **CS1** is a novel member of the CD2 subset that contains two of the unique tyrosine motifs present in 2B4 and SLAM. Signaling through 2B4, **CS1** and other members of the CD2 subset may play a major role in the regulation of **NK** cells and other leukocyte functions.

L5 ANSWER 3 OF 7 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2001143218 MEDLINE
DOCUMENT NUMBER: 21115149 PubMed ID: 11220635
TITLE: Molecular cloning of **CS1**, a novel human **natural killer** cell receptor belonging to the CD2 subset of the immunoglobulin superfamily.
AUTHOR: Boles K S; Mathew P A
CORPORATE SOURCE: Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth 76107-2699, USA.
CONTRACT NUMBER: AI 38938 (NIAID)
SOURCE: IMMUNOGENETICS, **(2001)** 52 (3-4) 302-7.
Journal code: 0420404. ISSN: 0093-7711.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF291815
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

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L5 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:278761 BIOSIS
DOCUMENT NUMBER: PREV200100278761
TITLE: Molecular cloning of **CS1**, a novel human **NK** cell receptor belonging to the CD2 subset of the immunoglobulin superfamily.
AUTHOR(S): Boles, Kent S. (1); Mathew, Porunelloor A. (1)
CORPORATE SOURCE: (1) University of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, TX, 76107 USA
SOURCE: FASEB Journal, (**March 7, 2001**) Vol. 15, No. 4, pp. A709. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Natural killer** (**NK**) cell cytolytic function and cytokine production are regulated by a delicate balance of signals transduced by activating and inhibitory receptors. Previous attention in the field has focused on MHC recognizing, receptors that are mostly inhibitory. However, members of the CD2 subset of receptors do not recognize MHC molecules, but still play a major role in **NK** and T cell functions. Two members of the CD2 subset, 2B4 (CD244) and SLAM (CD150), are involved in cellular activation such as lymphoproliferation, cytokine production, cytotoxicity, and invasiveness. The cytoplasmic domains of 2B4 and SLAM contain novel tyrosine motifs (TxYxxI/V/A) different from those observed in other **NK** and T cell receptors. The adaptor molecule SH2D1A/SAP (SLAM-associated protein) associates with these unique tyrosine motifs. Mutations in SAP result in dysregulated signaling through 2B4 and SLAM and may play a causative role in the often fatal X-linked lymphoproliferative (XLP) disease. Here we report the identification and characterization of **CS1**, a novel human **NK** cell receptor that contains two of the unique tyrosine motifs. Structural analysis indicates that **CS1** is a new member of the CD2 subset of the immunoglobulin superfamily of receptors. The extracellular domain of **CS1** contains tow 1g domains that show maximum homology to 2B4 and SLAM. The presence of the unique tyrosine motifs in the cytoplasmic domain of **CS1** suggests that it may associate with SAP and regulate immune responses. The **CS1** gene is located on human chromosome 1 at 1q23-24 between CD48 and Ly-9 (CD229) along with other members of the CD2 subfamily.

L13 ANSWER 15 OF 16 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 93315874 MEDLINE
DOCUMENT NUMBER: 93315874 PubMed ID: 8326140
TITLE: A novel function-associated molecule related to non-MHC-restricted cytotoxicity mediated by activated **natural killer** cells and T cells.
AUTHOR: Garni-Wagner B A; Purohit A; Mathew P A; Bennett M; Kumar V
CORPORATE SOURCE: Graduate Program in Immunology, University of Texas Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: AI-20451 (NIAID)
CA-36921 (NCI)
CA-36922 (NCI)
+
SOURCE: JOURNAL OF IMMUNOLOGY, **(1993 Jul 1)** 151 (1) 60-70.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930820
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Entered Medline: 19930812

AB **NK** cells and IL-2-propagated splenic T cells mediate non-MHC-restricted cytotoxicity. The molecules involved in this process are not well defined. We describe a novel 66-kDa cell surface molecule called 2B4 that is expressed on cells that mediate non-MHC-restricted cytotoxicity. All resting and rIL-2 cultured **NK** cells and a significant number of T cells cultured in high doses of rIL-2 are 2B4+. In fresh as well as cultured spleen cells, all non-MHC-restricted cytotoxicity is contained within the 2B4+ population. In addition to defining cells capable of non-MHC-restricted killing, the 2B4 molecule is also involved in modulation of their function. In the presence of **anti-2B4**, the lytic activity of cultured **NK** cells and non-MHC-restricted T cells against a wide variety of FcR- and FcR+ targets is greatly augmented. **Anti-2B4** is also able to transduce other signals in IL-2-activated **NK** cells such as IFN-gamma secretion and granule exocytosis. In addition, 2B4+ T cells can specifically lyse the 2B4 hybridoma cells. Unlike many other activation and adhesion molecules (such as murine CD2, LFA-1, and CD16), 2B4 expression is restricted to cells that mediate **NK**-like killing. Conversely, highly activated T cells that do not express 2B4 do not mediate non-MHC-restricted killing. Together these data suggest that the 2B4 molecule is likely to be a part of a receptor complex or a component of signal-transducing complex on cells that mediate non-MHC-restricted killing.

L13 ANSWER 16 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:448599 BIOSIS
DOCUMENT NUMBER: BR41:86334
TITLE: 2B4 ANTIGEN IS INVOLVED IN THE NON-MHC-RESTRICTED CYTOTOXICITY MEDIATED BY **NK** AND T CELLS.
AUTHOR(S): GARNI-WAGNER B A; PUROHIT A; BENNETT M; KUMAR V
CORPORATE SOURCE: UNIV. TEX. SOUTHWESTERN MED. CENT., DALLAS, TEX., USA.

SOURCE: SEVENTH INTERNATIONAL WORKSHOP ON NATURAL KILLER CELLS, STOCKHOLM (LIDINGO), SWEDEN, JUNE 4-7, 1991. NAT IMMUN CELL GROWTH REGUL, (1991) 10 (3), 173.
CODEN: NICRDR. ISSN: 0254-7600.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L13 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:219816 BIOSIS
DOCUMENT NUMBER: PREV199900219816
TITLE: Molecular characterization of a human **natural killer** cell receptor homologus to mouse 2B4.
AUTHOR(S): Boles, Kent (1); Stepp, Susan; Colonna, Marco; Bennett, Michael; Kumar, Vinay; Mathew, Porunelloor (1)
CORPORATE SOURCE: (1) Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, TX, 76107 USA
SOURCE: Natural Immunity, (**Feb.**, **1998**) Vol. 16, No. 2-3, pp. 75.
Meeting Info.: Fifth Annual Meeting of the Society for Natural Immunity Seventeenth International Natural Killer Cell Workshop Warrenton, Virginia, USA October 17-21, 1998
ISSN: 1018-8916.
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L13 ANSWER 11 OF 16 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999385502 MEDLINE
DOCUMENT NUMBER: 99385502 PubMed ID: 10458320
TITLE: Molecular characterization of a novel human **natural killer** cell receptor homologous to mouse 2B4.
AUTHOR: Boles K S; Nakajima H; Colonna M; Chuang S S; Stepp S E; Bennett M; Kumar V; Mathew P A
CORPORATE SOURCE: Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth 76107-2699, USA.
CONTRACT NUMBER: PO1 AI 38938 (NIAID)
SOURCE: TISSUE ANTIGENS, **(1999 Jul)** 54 (1) 27-34.
Journal code: 0331072. ISSN: 0001-2815.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991006

AB **Natural killer** (**NK**) cells spontaneously detect and kill cancerous and virally infected cells through receptors that transduce either activating or inhibiting signals. The majority of well studied **NK** receptors are involved in inhibitory signaling. However, we have previously described an activating receptor, 2B4, expressed on all murine **NK** cells and a subset of T cells that mediate non-major histocompatibility complex (MHC) restricted killing. **Anti-2B4** monoclonal **antibodies** directed against IL-2-activated **NK** cells enhanced their destruction of tumor cells. Recently, we determined binding of 2B4 to CD48 with a much higher affinity than CD2 to CD48. Here we describe the molecular characterization of a cDNA clone homologous to mouse 2B4, isolated from a human **NK** cell library. The cDNA clone contained an open reading frame encoding a polypeptide chain of 365 amino acid residues. The predicted protein sequence showed 70% similarity to murine 2B4. Additionally, it has 48, 45, and 43% similarity to human CD84, CDw150 (SLAM), and CD48, respectively. RNA blot analysis indicates the presence of 3 kb and 5 kb transcripts in T- and **NK**-cell lines. A single transcript of 3 kb is identified in poly(A)+ RNA from human spleen, peripheral blood leukocytes, and lymph node, whereas, the level of expression in bone marrow and fetal liver was indeterminate. Preliminary functional data suggests that **NK**-cell interaction with target cells via 2B4 modulates human **NK**-cell cytolytic activity.

L13 ANSWER 8 OF 16 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000203434 MEDLINE
DOCUMENT NUMBER: 20203434 PubMed ID: 10741393
TITLE: 2B4 functions as a co-receptor in human **NK** cell activation.
AUTHOR: Sivori S; Parolini S; Falco M; Marcenaro E; Biassoni R; Bottino C; Moretta L; Moretta A
CORPORATE SOURCE: Dipartimento di Medicina Sperimentale, Universita degli Studi di Genova, Italy.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, **(2000 Mar)** 30 (3) 787-93.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000419

AB Natural cytotoxicity receptors (NKp46, NKp44 and NKp300) play a predominant role in human **NK** cell triggering during natural cytotoxicity. Human 2B4 also induced **NK** cell activation in redirected killing assays using **anti-2B4** monoclonal **antibodies** (mAb) and murine targets. Since this effect was confined to a fraction of **NK** cells, this suggested a functional heterogeneity of 2B4 molecules. Here we show that activation via 2B4 in redirected killing against murine targets is strictly dependent upon the engagement of NKp46 by murine ligand (s) on target cells. Thus, **NK** cell clones expressing high surface density of NKp46 (NKp46bright) were triggered by **anti-2B4** mAb, whereas NKp46dull clones were not although they expressed a comparable surface density of 2B4. mAb-mediated modulation of NKp46 molecules in NKp46bright clones had no effect on the expression of 2B4 while it rendered cells unresponsive to **anti-2B4** mAb. Finally, **anti-2B4** mAb could induce **NK** cell triggering in NKp46dull clones provided that suboptimal doses of anti-NKp44 or anti-CD16 mAb were added to the redirected killing assay. These results indicate that differences in responses do not reflect a functional heterogeneity of 2B4 but rather depend on the co-engagement of triggering receptors.

L13 ANSWER 5 OF 16 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001103152 MEDLINE
DOCUMENT NUMBER: 20586144 PubMed ID: 11169415
TITLE: Analysis of the molecular mechanism involved in 2B4-mediated **NK** cell activation: evidence that human 2B4 is physically and functionally associated with the linker for activation of T cells.
AUTHOR: Bottino C; Augugliaro R; Castriconi R; Nanni M; Biassoni R;
Moretta L; Moretta A
CORPORATE SOURCE: Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.. bottino@ermes.cba.unige.it
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, **(2000 Dec)** 30 (12) 3718-22.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
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Entered Medline: 20010126

AB While 2B4 is a well-known surface receptor involved in **NK** cell triggering and induction of cytotoxicity against CD48-positive target cells, little is known about the downstream events which lead to **NK** cell activation. In this study we show that, in normal human **NK** cells, 2B4 constitutively associates with the linker for activation of T cells (LAT). **Antibody**-mediated engagement of **2B4** resulted in tyrosine phosphorylation not only of 2B4 but also of the associated LAT molecules. Moreover, tyrosine phosphorylation of LAT led to the recruitment of intracytoplasmic signaling molecules including phospholipase Cgamma and Grb2. These data support the concept that 2B4 may mediate **NK** cell triggering via a LAT-dependent signaling pathway.

L13 ANSWER 6 OF 16 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000483195 MEDLINE
DOCUMENT NUMBER: 20432266 PubMed ID: 10975798
TITLE: Functional requirement for SAP in 2B4-mediated activation of human **natural killer** cells as revealed by the X-linked lymphoproliferative syndrome.
AUTHOR: Tangye S G; Phillips J H; Lanier L L; Nichols K E
CORPORATE SOURCE: Centenary Institute for Cancer Medicine and Cell Biology, and University of Sydney, New South Wales, Australia.. s.tangye@centenary.usyd.edu.au
SOURCE: JOURNAL OF IMMUNOLOGY, **(2000 Sep 15)** 165 (6) 2932-6.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001010

AB X-linked lymphoproliferative syndrome (XLP) is an immunodeficiency characterized by life-threatening infectious mononucleosis and EBV-induced B cell lymphoma. The gene mutated in XLP encodes SLAM (signaling lymphocytic activation molecule-associated protein)-associated protein (SAP), a small SH2 domain-containing protein. SAP associates with 2B4 and SLAM, activating receptors expressed by **NK** and T cells, and prevents recruitment of SH2 domain-containing protein tyrosine phosphatase-2 SHP-2) to the cytoplasmic domains of these receptors. The phenotype of XLP may therefore result from perturbed signaling through SAP-associating receptors. We have addressed the functional consequence of SAP deficiency on 2B4-mediated **NK** cell activation. Ligating 2B4 on normal human **NK** cells with **anti-2B4** mAb or interaction with transfectants bearing the 2B4 ligand CD48 induced **NK** cell cytotoxicity. In contrast, ligation of 2B4 on **NK** cells from a SAP-deficient XLP patient failed to initiate cytotoxicity. Despite this, CD2 or CD16-induced cytotoxicity of SAP-deficient **NK** cells was similar to that of normal **NK** cells. Thus, selective impairment of 2B4-mediated **NK** cell activation may contribute to the immunopathology of XLP.

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